VERIFICATION OF TRANSLATION

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Signed this 12th day of February, 2009

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[DOCUMENT TITLE] APPLICATION FOR PATENT
[DOCKET NUMBER] P99-1031
[FILING DATE] February 10, 2000
[DESTINATION] Commissioner, Patent Office
[INTERNATIONAL PATENT CLASSIFICATION] A61K 31/00
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[INDICATION RELATING TO FEES]
[Prepayment Register Number] 009977
[Amount of Payment] 21000

[LIST OF MATERIALS FILED]

[Material Name]	Specification	1
[Material Name]	Drawing	1
[Material Name]	Abstract	1

[GENERAL POWER OF ATTORNEY NUMBER] 9706372

[REQUEST FOR PROOF] Required

[DOCUMENT TITLE] SPECIFICATION
[TITLE OF INVENTION] AUTONOMIC NERVE REGULATING AGENT
[SCOPE OF PATENT CLAIM]

[Claim 1] An autonomic nerve regulating agent, comprising a sesquiterpene alcohol with a boiling point of 250°C or higher.

[Claim 2] The autonomic nerve regulating agent according to Claim 1, wherein said sesquiterpene alcohol is cedrol.

[Claim 3] A sleep improving agent, comprising a sesquiterpene alcohol with a boiling point of 250°C or higher.

[Claim 4] The sleep improving agent according to Claim 3, wherein said sesquiterpene alcohol is cedrol.

[DETAIL DESCRIPTION OF THE PRESENT INVENTION]

[0001]

[TECHNICAL FIELD OF THE INVENTION]

The present invention relates to an autonomic nerve regulating agent having sedative action and sleep improving action.

[0002]

[PRIOR ART]

When the balance between the activities of the parasympathetic nervous system and the sympathetic nervous system is upset by physical and mental stress, the resulting disequilibrium in the autonomic nervous system can lead to mental aggravation, making it difficult to fall asleep very easily (sleep induction) and resulting in shallow sleep. It is believed that stimulating the physiological predominance of the parasympathetic activity over the sympathetic activity can reduce stress and calm aggravated mental states, thus inducing favorable sleep.

[0003]

Methods that have long been used to thus stimulate the predominance of the parasympathetic activity over the sympathetic activity include the oral or percutaneous

administration of active ingredients to humans, as well as aromatherapy involving vaporizable fragrance compositions to allow the vapors to be inhaled. Recent proposals include methods in which bitter orange essential oil (JP-A-H4-128234) and jasmine lactone (JP-A-H6-40911) are administered by absorption via the nasal mucosa, oral mucosa, or pulmonary tissue for better sleep induction.

[0004]

The use of the low-boiling components of cedar wood oil (such as α-pinene, α-cedrene, β-cedrene, and caryophyllene) as a sedative essential oil has also been proposed (JP-A-H5-255688).

[0005]

[Problems Which the Invention Is Intended to Solve]

However, there is substantial individual variation in the sensitivity to and preference for scents (fragrances) such as bitter orange essential oil and jasmine lactone. While these may have sedative and sleep inducing action for some people, they may on the contrary be disagreeable or irritating to others. There is thus a need for a component or method capable of universally improving autonomic nervous imbalances (in other words, restoring the balance to a physiologically normal range).

[0006]

The low-boiling components of cedar wood oil have a strongly characteristic fragrance, and their sedative actions are also subject to considerable individual variation in terms of people's sensitivity and preferences in the same manner as bitter orange essential oil and the like.

[0007]

An object of the present invention is to provide an autonomic nerve regulating agent, which have a sedative action and sleep improving action for individuals whose sympathetic activity is predominant, irrespective of the variation in individual sensitivity or preference for fragrances, and

conversely have action in restoring the physiological balance to within normal range in individuals whose parasympathetic activity is predominant.

[0008]

[Means Used to Solve the Above-Mentioned Problems]

The inventors have discovered that some compounds, which belong to sesquiterpene alcohols, are substantially odorless, that nevertheless, they have sedative or sleep improving action on individuals whose sympathetic activity is predominant (said action stimulating the predominance of the parasympathetic activity over the sympathetic activity), and that they conversely have action in stimulating the predominance of the sympathetic activity over the parasympathetic activity to restore the physiological balance to within normal range in individuals whose parasympathetic activity is predominant.

[0009]

That is, the present invention provides an autonomic nerve regulating agent, comprising sesquiterpene alcohol with a boiling point of 250°C or higher. In particular, the autonomic nerve regulating agent of the present invention is useful as a sleep improving agent.

[0010]

[Embodiments of the Invention]

The autonomic nerve regulating agent of the present invention comprises a sesquiterpene alcohol with a boiling point of 250°C or higher at atmospheric pressure, as compounds which have sedative action and sleep improving action for individuals whose sympathetic activity is predominant, and which conversely have action in stimulating the sympathetic activity to predominance over the parasympathetic activity in individuals whose parasympathetic activity is predominant.

[0011]

Examples of sesquiterpene alcohols with a boiling point of 250°C or higher include cedrol (boiling point 295°C), cedrenol (boiling point 270°C), farnesol (boiling point 263°C), patchouli alcohol (boiling point 140°C/8 mmHg), eugenol

(boiling point 254-255°C), α-santalol (boiling point 302°C), α-bisabolol (boiling point 265°C), β-caryophyllene alcohol (boiling point 287-297°C), vetiverol (boiling point 264°C), sclareol (boiling point 340°C or higher), geranyl linalool (boiling point 340°C), isophytol (boiling point 310°C or higher), and nerolidol (boiling point 276°C), as well as globulol and guaiol. Of these, cedrol is preferred because it is odorless, affords excellent effects in the invention and is readily available.

[0012]

The amount of the sesquiterpene alcohol with a boiling point of 250°C or higher (at atmospheric pressure) that is used in the present invention can be determined as desired according to the intended application of the autonomic nerve regulating agents (such as fragrance components, base cosmetics, make-up cosmetics, hair cosmetics, bathing agents, poultices, massaging agents, indoor fragrances, and sleep improving agents) or according to the formulation that is used (such as solutions, solids, powders, sprays, gels, and pastes). When used as a lotion, for example, the amount is preferably 0.01 to 0.05 wt% in consideration of the dissolution stability of the sesquiterpene alcohol. When used as an emulsion or cream, the amount is preferably 0.01 to 7.50 wt% in the consideration of the emulsion stability. When used in the form of a bathing agent, the type of formulation and the amount may be selected so as to result in a concentration of at least 0.01 ppm, preferably 0.1 to 1000 ppm, and even more preferably 5 to 1000 ppm, in the bath water.

[0013]

Various additives commonly used in a variety of applications (such as oils, fillers, colorants, polymers, humectants, UV absorbents, pH adjusting agents, antioxidants, surfactants, and fragrances) can be blended as desired in the autonomic nerve regulating agent of the present invention according to the intended application and the formulation that is used.

[0014]

The autonomic nerve regulating agent of the present invention can be administered to humans through respiration, , orally or transdermal penetration.

[0015]

The method of using the autonomic nerve regulating agent of the present invention can also be determined as desired according to the intended application and the formulation that is used. For example, when used in the form of a pad soaked with a sesquiterpene alcohol having a boiling point of 250°C or higher, the pad may be heated by electric heater to allow the sesquiterpene alcohol to be vaporized in the air. In this case, the sesquiterpene alcohol should be vaporized at a concentration of between 0.01 to 100 ppb in the air, as too low a concentration will not afford the desired results, while too high a concentration will result in the condensation of fine particles in the air.

[0016]

As noted above, the autonomic nerve regulating agent in the present invention is capable of mitigating physical or mental stress and of smoothing aggravated mental states. Also it is capable of prolonging the period of deep sleep (non-REM sleep), and improving the quality of sleep. The autonomic nerve regulating agent of the present invention is thus suitable for use as a sleep improving agent.

[0017]

The use of an odorless compound, particularly cedrol, from among the sesquiterpene alcohols employed in the present invention allows the autonomic nerve regulating agent of the present invention to produce the aforementioned effects in individuals or an unspecified number of individuals, regardless of their disposition towards fragrances. The autonomic nerve regulating agent of the present invention can accordingly be used in public spaces (halls, hospitals, stations, and business offices), in any configuration.

[0018]

[Examples]

The present invention is illustrated in further detail in the following examples.

[0019]

Example 1

The subjects were ten women in their twenties complaining of fatigue (sympathetic overactivity), who were asked to inhale cedrol dissolved in dipropylene glycol (10 wt% concentration), while ECG at rest (chest V5 lead), blood pressure (tonometry), and respiration (pulmonary volume instantaneously measured by respiratory rate sensor) were monitored. The changes in parameters before and after measurement were compared. Frequency analysis of R-R interval fluctuations was performed for low frequency components integrating amplitudes 0.02 to 0.12 Hz (sum of low frequency: Lsum) and high frequency components integrating amplitudes 0.12 to 2.00 Hz (sum of high frequency: Hsum) using the rapid Fourier transform.

[0020]

The measurement results were statistically analyzed by Welch's t test or Student's t test based on the F test.

[0021]

Results

1) The systolic blood pressure (SBP) was meaningfully lower (5%) after inhalation compared to before inhalation (Fig. 1(a)).

[0022]

2) The diastolic blood pressure (DBP) was meaningfully lower (5%) after inhalation compared to before inhalation (Fig. 1(b)).

[0023]

3) The ECG R-R interval was meaningfully longer (5%) after inhalation compared to before inhalation (Fig. 1(c)).

[0024]

4) The Hsum was meaningfully greater (5%) after inhalation compared to before inhalation (Fig. 1(d)).

[0025]

5) The Lsum/Hsum was meaningfully lower (5%) after inhalation compared to before inhalation (Fig. 1(e)).

[0026]

6) The respiratory rate (RR) was meaningfully lower (5%) after inhalation compared to before inhalation (Fig. 1(f)).

[0027]

Conclusions

The above results demonstrate that the inhalation of cedrol by the subjects resulted in sedative effects in various parts of the body, suppressed sympathetic overactivity, and resulted in the predominance of the parasympathetic activity.

[0028]

Example 2

The subjects were ten insomniac women in their twenties (under considerable pressure to get to sleep, with parasympathetic predominance to excess), who were asked to inhale cedrol dissolved in dipropylene glycol (10 wt% concentration), while ECG at rest (chest V5 lead), blood pressure (tonometry), and respiration (pulmonary volume instantaneously measured by respiratory rate sensor), and skin blood flow of forehead (measured by laser Doppler methods) were monitored. The changes in parameters before and after measurement were compared. Frequency analysis of R-R interval fluctuations and statistical analysis of the measurement results were done in the same manner as in Example 1.

[0029]

Results

1) The systolic blood pressure (SBP) was meaningfully higher (5%) (within physiologically normal range) after inhalation compared to before inhalation (Fig. 2(a)).

[0030]

2) The diastolic blood pressure (DBP) was meaningfully higher (5%) (within physiologically normal range) after inhalation compared to before inhalation (Fig. 2(b)).

[0031]

3) There was no meaningful change in ECG R-R interval after

inhalation compared to before inhalation (Fig. 2(c)).

[0032]

4) The Hsum tended to be lower after inhalation compared to before inhalation (Fig. 2(d)).

[0033]

5) The Lsum/Hsum tended to be higher after inhalation compared to before inhalation (Fig. 2(e)).

[0034]

6) There was no meaningful difference in respiratory rate (RR) after inhalation compared to before inhalation (Fig. 2(f)).

[0035]

Conclusion

The above results demonstrate that the inhalation of cedrol by the subjects resulted in a return to a state of equilibrium in various parts of the body, and suppressed parasympathetic overactivity while simultaneously elevating the sympathetic underactivity, thereby resulting in a suitable autonomic nervous balance.

[0036]

Example 3

The subjects were ten women in their twenties suffering from poor sleep. ECG (chest V5 lead), brain waves (C3, O1 in the international 10-20 method), respiration (impedance method: abdomen and chest), superficial electromyogram (bipolar lead of left and right mentalis muscles), and ocular movement (bipolar lead without horizontally linking left and right eye-sockets) were monitored from the time the subjects went to bed until they woke in a 40 m^2 room. The cedrol was administered by placing Petri dishes filled with cedrol on 95°C hot plates so that approximately 100 mg was vaporized per hour, from the time subjects went to bed until they woke. Measurements were taken for 7 days. No administration took place on the first two days, in order to allow subjects to become acclimated to the measuring instruments and environment (control). On the third day, administration was managed

without anything placed on the hot plates (placebo). After 3 days, Cedrol was administered on the 7th day.

[0037]

The subjects were interviewed about their condition on waking using a questionnaire based on POMS (profile of mood states) to assess mood. The changes in the parameters measured during the administration of cedrol and placebo treatment were compared. Awakening and sleep stages were determined in accordance with international standards for determining sleep stages (*Sleep Brain Wave Atlas*, pp. 3-9, Ishiyaku Shuppan KK, published September, 1971).

[0038]

Results

1) Hsum was meaningfully increased (5%) during non-REM sleep when cedrol was administered compared to the placebo treatment (Fig. 3(a)).

[0039]

2) The cumulative incidence of stages 3 and 4 of sleep was meaningfully greater (5%) when cedrol was administered compared to the placebo treatment (Fig. 3(b)).

[0040]

3) The respiratory rate (RR) was meaningfully lower (5%) during non-REM sleep when cedrol was administered compared to the placebo treatment (Fig. 3(c)).

[0041]

4) POMS revealed meaningful (5%) improvement in tension and fatigue when cedrol was administered on the 7th day compared to before administration and the 3rd day (placebo treatment) (Fig. 3(d)).

[0042]

Conclusion

The above results reveal that subjects who slept while inhaling the fumes of cedrol (100 mg/hr) had a meaningfully deeper sleep, a longer non-REM sleep cycle, and a better quality of sleep, indicating a shift to parasympathetic predominance.

[0043]

Example 4

The subjects were ten women in their twenties experiencing fatigue (sympathetic overactivity), who were asked to massage their faces as shown in Fig. 1 of Japanese Laid-Open Patent Application (Kokai) H10-113369 using the massage cream preparation in Table 1 once a day before sleep for 4 continuous weeks. Specifically, as shown in Fig. 4, (step 1) approximately 2 mL massage cream was spread on the hands and applied to the face, (step 2) the face was massaged 2 to 3 times with all four fingers (index to pinky) of both hands in a line from the corners of the mouth to the wings of the nose (direction (a) in Fig. 4), (step 3) the face was massaged 2 to 3 times in circles outward from the center of the cheeks (direction (b) in Fig. 4), (step 4) the face was massaged 2 to 3 times in arcs outward from the center of the forehead (direction (c) in Fig. 4), (step 5) steps 2 through 4 were repeated 3 times, and (step 6) the face under the eyes was massaged 3 times in arcs gradually extending outward (direction (d) in Fig. 4).

[0044]

The ECG at rest (chest V5 lead), blood pressure (tonometry), and respiration (pulmonary volume instantaneously measured by respiratory rate sensor) were monitored in the morning before and 4 weeks after the beginning of massaging, so as to compare changes in the parameters. Frequency analysis of R-R interval fluctuations and statistical analysis of the measurement results were done in the same manner as in Example 1.

[0045]

[Table 1]

Components	Wt%
Oil components:	
beeswax	6.0
cetanol	5.0
reduced lanolin	8.0
squalane	37.5
fatty acid glycerin	4.0
Emulsifiers:	
oleophilic glycerin monostearate	2.0
polyoxyethylene (20 EO) sorbitan laurate ester	2.0
Aqueous phase:	
propylene glycol	5.0
purified water	30.0
cedrol	0.5
preservative/antioxidant	proper amount

[0046]

Results

1) The systolic blood pressure (SBP) was meaningfully lower (5%) 4 weeks after the beginning of massaging compared to before massaging (Fig. 5(a)).

[0047]

2) The diastolic blood pressure (DBP) was meaningfully lower (5%) 4 weeks after the beginning of massaging compared to before massaging (Fig. 5(b)).

[0048]

3) The ECG R-R interval was meaningfully longer (5%) 4 weeks after the beginning of massaging compared to before massaging (Fig. 5(c)).

[0049]

4) The Hsum was meaningfully higher 4 weeks after the beginning of massaging compared to before massaging (Fig.

5(d)).

[0050]

5) The Lsum/Hsum was meaningfully lower 4 weeks after the beginning of massaging compared to before massaging (Fig. 5(e)).

[0051]

6) The respiratory rate (RR) was meaningfully lower (5%) 4 weeks after the beginning of massaging compared to before massaging (Fig. 5(f)).

[0052]

Conclusion

The above results reveal that massaging the face using massage cream containing a cedrol blend once a day for 4 continuous weeks resulted in sedative effects in various parts of the body, the suppression of sympathetic overactivity, and a shift to parasympathetic predominance.

[0053]

[Merits of the Invention]

The autonomic nerve regulating agent of the present invention comprises a sesquiterpene alcohol with a boiling point of 250°C or higher (at atmospheric pressure), and acts on individuals without any noticeable perception of odor, thereby bringing about the relative predominance of the parasympathetic activity over the sympathetic activity in individuals with sympathetic overactivity (that is, sympathetic suppression and/or parasympathetic stimulation). The invention can stimulate the predominance of the parasympathetic activity over the sympathetic activity, regardless of individual sensitivity to or preference for fragrances, can normalize autonomic nerve disequilibrium, and has favorable effects on individuals such as sedative action and sleep improving action.

[0054]

The autonomic nerve regulating agent of the present invention can stimulate the predominance of the sympathetic activity over the parasympathetic activity to restore the

physiological balance to within normal range in individuals whose parasympathetic activity is predominant.

[Brief Description of the Drawings]

[Fig. 1]

Fig. 1 illustrates the measurement results for the various test parameters of the autonomic nerve regulating agent in Example 1.

[Fig. 2]

Fig. 2 illustrates the measurement results for the various test parameters of the autonomic nerve regulating agent in Example 2.

[Fig. 3]

Fig. 3 illustrates the measurement results for the various test parameters of the autonomic nerve regulating agent (sleep improving agent) in Example 3.

[Fig. 4]

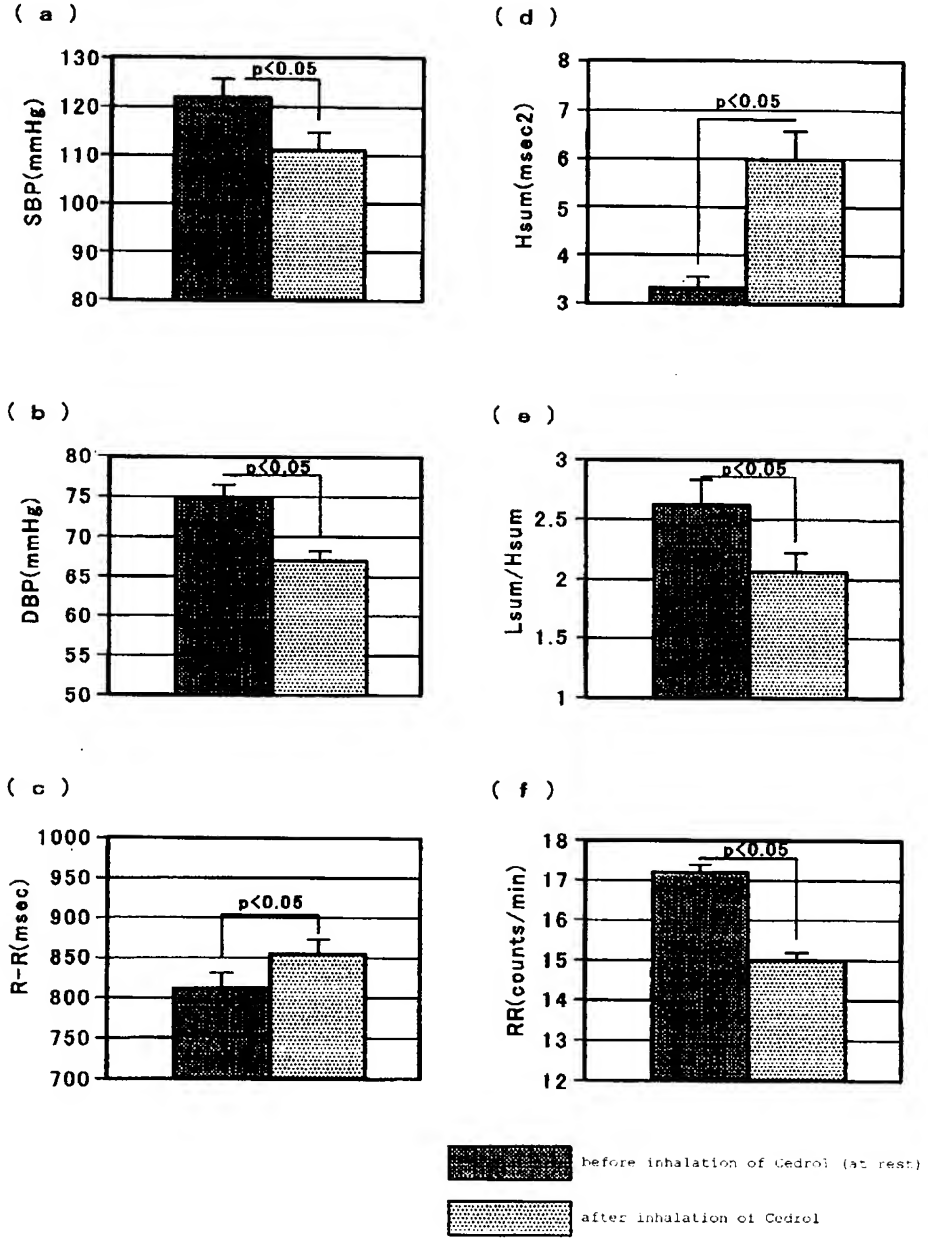
Fig. 4 illustrates a method for massaging the face.

[Fig. 5]

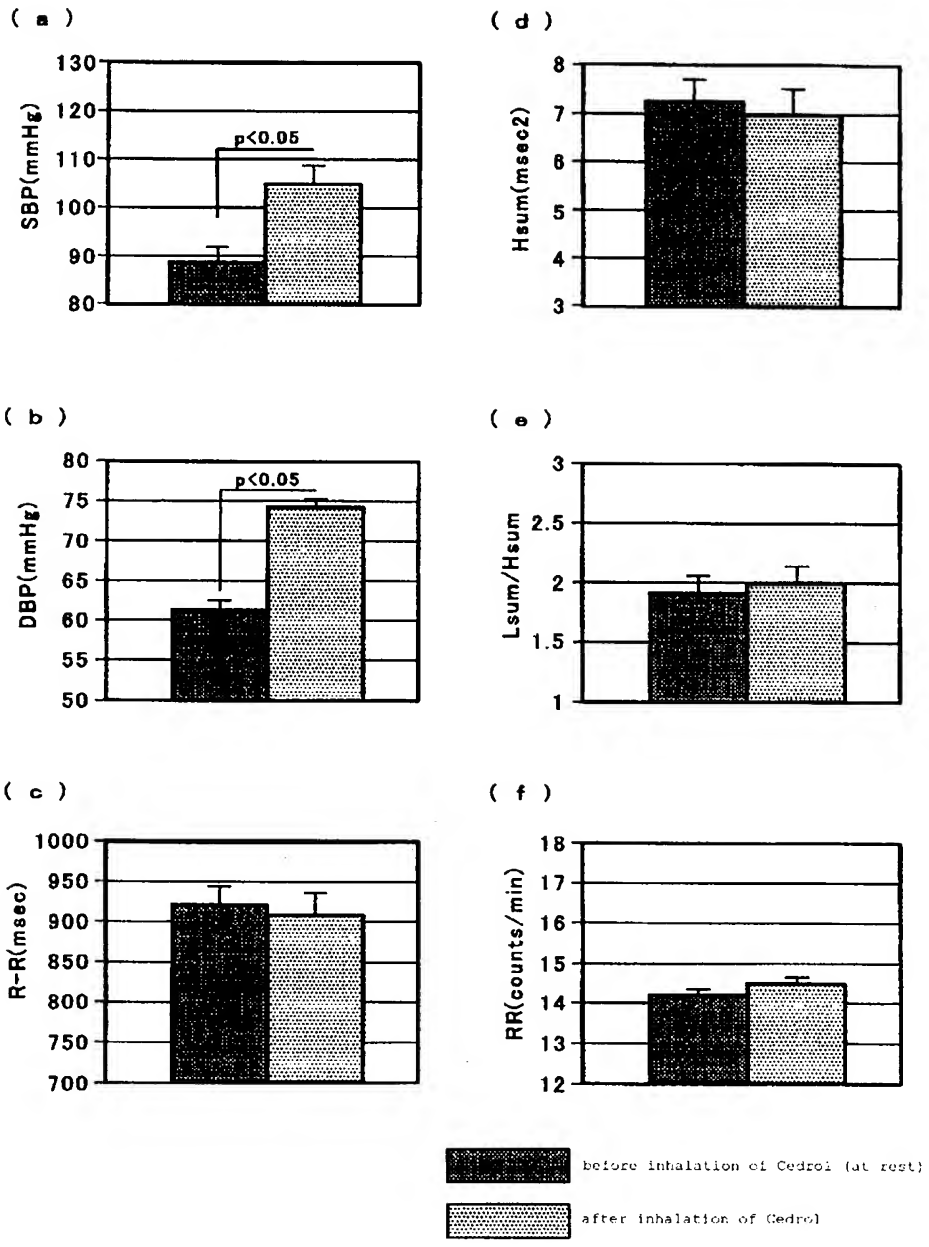
Figs. 5 illustrates the measurement results for the various test parameters of the autonomic nerve regulating agent (massaging agent) in Example 4.

[DRAWINGS]

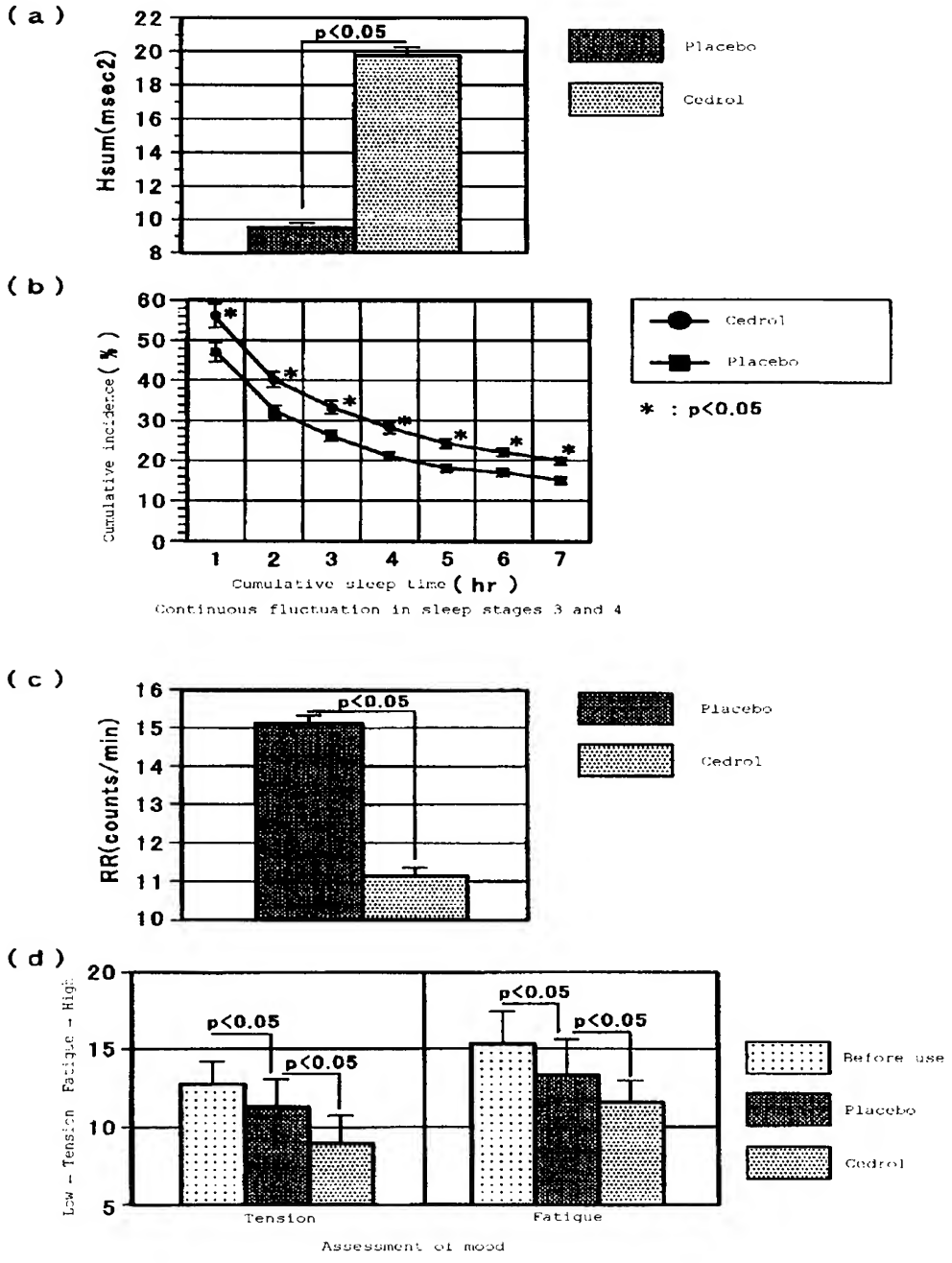
[FIG. 1]



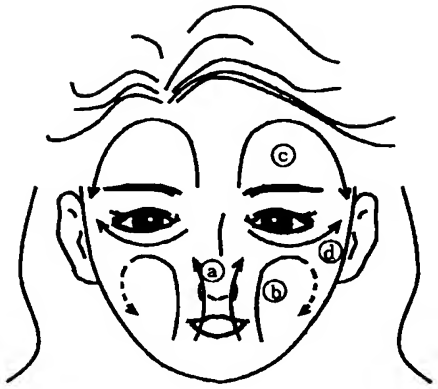
[FIG. 2]


(a)
SBP(mmHg)
130
120
110
100
90
80
p<0.05
(b)
DBP(mmHg)
80
75
70
65
60
55
50
p<0.05
(c)
R-R(msec)
1000
950
900
850
800
750
700
(d)
Hsum(msec2)
8
7
6
5
4
3
(e)
Lsum/Hsum
3
2.5
2
1.5
1
(f)
RR(counts/min)
18
17
16
15
14
13
12
before inhalation of Cedrol (at rest)
after inhalation of Cedrol

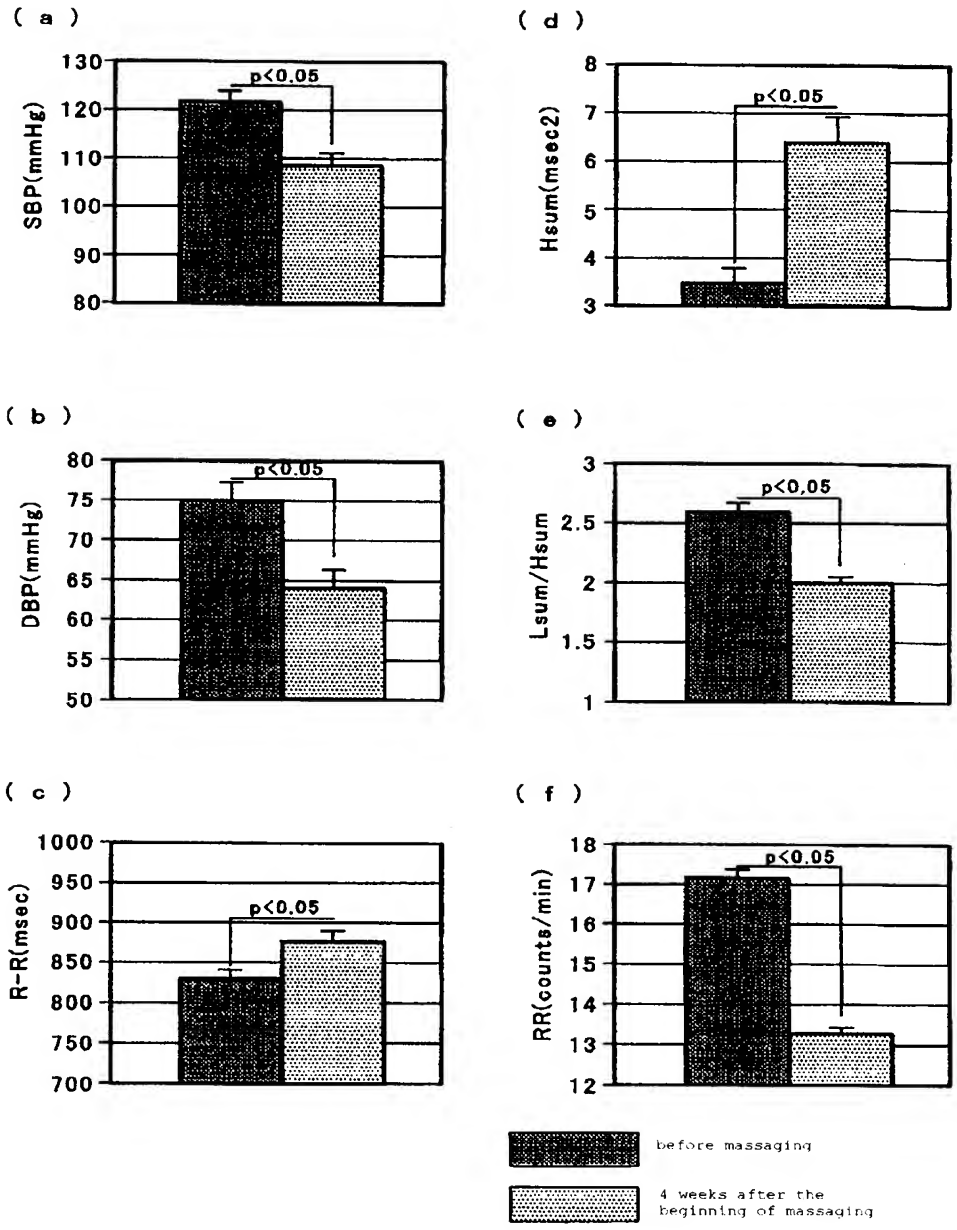
[FIG. 3]


(a)
Hsum(msec2)
p<0.05
Placebo
Cedrol
(b)
Cumulative incidence (%)
Cumulative sleep time (hr)
Cedrol
Placebo
* : p<0.05
Continuous fluctuation in sleep stages 3 and 4
(c)
RR(counts/min)
p<0.05
Placebo
Cedrol
(d)
Low - Tension Fatigue - High
p<0.05
p<0.05
p<0.05
p<0.05
Tension
Fatigue
Assessment of mood
Before use
Placebo
Cedrol

[FIG. 4]



[Fig. 5]


(a)
SBP(mmHg)
130
120
110
100
90
80
p<0.05
(b)
DBP(mmHg)
80
75
70
65
60
55
50
p<0.05
(c)
R-R(msec)
1000
950
900
850
800
750
700
p<0.05
(d)
Hsum(msec2)
8
7
6
5
4
3
p<0.05
(e)
Lsum/Hsum
3
2.5
2
1.5
1
p<0.05
(f)
RR(counts/min)
18
17
16
15
14
13
12
p<0.05
before massaging
4 weeks after the beginning of massaging

[DOCUMENT TITLE] ABSTRACT

[Abstract]

[Object] The autonomic nerve regulating agent of the present invention, which has a sedative action and sleep inducing action in individuals, regardless of individual variation in sensitivity to or preference for fragrance.

[Means] The autonomic nerve regulating agent of the present invention contains as an active ingredient a sesquiterpene alcohol with a boiling point of 250°C or higher, particularly cedrol.

[Selected Figure] None